Telaprevir (Incivek™)

Criteria for Use

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VA Pharmacy Benefits Management Services, Medical Advisory Panel, VISN Pharmacist Executives,
Public Health Strategic Healthcare Group and Hepatitis C Resource Centers

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.** *The Product Information should be consulted for detailed prescribing information. See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://vaww.pbm.va.gov for further information.*

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive telaprevir.*

☐ Any contraindications to peginterferon and ribavirin apply since telaprevir must be administered with peginterferon and ribavirin (refer to VA HCRC and PHSHG HCV Treatment Recommendations for contraindications specific to peginterferon and ribavirin, http://vaww.hepatitis.va.gov)

☐ Documented ongoing nonadherence to prior medications, medical treatment or failure to complete HCV disease evaluation appointments and procedures

☐ Previous virologic failure with a boceprevir- or telaprevir- containing regimen (intolerance does not constitute failure)

☐ Patient infected with HIV (Limited safety and efficacy data; significant drug-drug interactions with certain antiretroviral agents)

☐ Patient with recurrent post-transplant HCV infection (No efficacy and safety data; significant drug-drug interactions with certain immunosuppressants)

☐ Decompensated liver disease (i.e., Child-Pugh score ≥7, MELD score >18, and/or clinical manifestations)

☐ Known hypersensitivity to telaprevir or any other component of telaprevir

☐ Known pregnancy, positive pregnancy test or in men whose female partners are pregnant or plan to become pregnant (Ribavirin is Category X)

☐ Coadministration with drugs that are highly dependent on CYP3A4 for clearance, **and** for which elevated plasma concentrations are associated with serious and/or life-threatening events (e.g, ergot derivatives, lovastatin, simvastatin, triazolam)

☐ Potent CYP3A4 inducers where significantly reduced telaprevir plasma concentrations may be associated with reduced efficacy (e.g., rifampin, carbamazepine, phenobarbital, phenytoin, St. John's Wort).

Inclusion Criteria *The answers to all of the following must be fulfilled in order to meet criteria.*

☐ **Will receive telaprevir in combination with peginterferon and ribavirin**

☐ Under care of and/or in collaboration with an experienced VA HCV practitioner

☐ Provider has discussed with patient the potential risks and benefit of HCV therapy and progression of HCV disease and a shared decision has been made for use

☐ Adherence counseling performed and documented understanding by patient

AND

☐ Chronic Infection with Hepatitis C Virus **genotype 1** with no previous treatment (i.e., treatment-naïve)

OR

☐ Chronic Infection with Hepatitis C Virus **genotype 1** who have previously received peginterferon and ribavirin but did not achieve a sustained virologic response (i.e., treatment–experienced)

For women of childbearing potential (this applies to female patients or in female partners of male patients),:

☐ Because telaprevir must be used in combination with ribavirin therapy (which is pregnancy category X) it should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Systemic oral contraceptives may not be as effective in women taking telaprevir; hence, it is recommended that two alternative effective methods of contraception, including intrauterine devices and barrier methods, should be used in women during treatment with telaprevir and concomitant ribavirin, and for 6 months after treatment has concluded.

Dosage, Administration and Response Guided Therapy

Prescriptions should be limited to a 28-day supply. Tablets can be stored at room temperature between 59-86ºF (15-30ºC).

Telaprevir 750 mg orally (2 x 375mg tablets) every 8 hours with food (not low fat) for 12 weeks *plus* peginterferon (either peginterferon alfa-2a 180 mcg/week or alfa-2b 1.5 mcg/kg/week) and ribavirin (in 2 divided doses) with food: <75 kg: 1000 mg/day or ≥75 kg: 1200 mg/day; alternative weight-based ribavirin dosing: <65 kg: 800 mg/day, 65-85 kg: 1000 mg/day, >85-105 kg: 1200 mg/day, >105 kg: 1400 mg/day.

Telaprevir must be administered with a high fat meal or snack containing at least 20 grams of fat. The high fat meal or snack should be ingested within 30 minutes prior to each telaprevir dose. Examples of some foods include a bagel with cream cheese, 0.5 cup nuts, 3 tablespoons peanut butter, 1 cup ice cream, 2 ounces American or cheddar cheese, 2 ounces potato chips, or 1.5 cup trail mix.

Treatment duration is guided by on-treatment HCV RNA response and patient characteristics as described in the Table below.

Population	**HCV RNA Assessment**[a]			**Regimen**	**Total treatment duration**
	Week 4	**Week 12**	**Week 24**		
Treatment-naïve (without cirrhosis) **OR** **Prior Relapser**[b]	Undetectable	Undetectable	Undetectable	Telaprevir plus PEG/riba for 12 weeks, then PEG/riba for an additional 12 weeks	24 weeks
	Detectable but ≤1000 IU/mL	Undetectable or Detectable but ≤1000 IU/mL	Undetectable	Telaprevir plus PEG/riba for 12 weeks, then PEG/riba for an additional 36 weeks	48 weeks
Compensated Cirrhosis (Treatment- naïve or -experienced) **OR** **Prior Partial Responder**[c] **OR** **Prior Null Responder**[d]	Undetectable or detectable but ≤1000 IU/mL	Undetectable or detectable but ≤1000 IU/mL	Undetectable	Telaprevir plus PEG/riba for 12 weeks, then PEG/riba for an additional 36 weeks	48 weeks
Treatment Futility	**If >1000 IU/mL, discontinue all treatment**	**If >1000 IU/mL, discontinue all treatment**	**Detectable at Week 24 or at any timepoint thereafter; discontinue all treatment**	**See recommended monitoring for further details**	

[a]A sensitive real-time quantitative HCV RNA assay with a lower limit of detection of <10-15 IU/mL should be used for decision making to determine treatment duration with response guided therapy.
[b]Relapser=undetectable HCV-RNA at end of prior treatment with a subsequent detectable HCV-RNA in plasma
[c]Partial responder=decrease in HCV-RNA viral load greater than or equal to 2-log10 by Week 12, but never achieved SVR
[d]Null Responder=decrease of <2 $\log_{10}$ in HCV viral load after 12 weeks of prior HCV therapy with peginterferon and ribavirin
PEG=peginterferon, riba=ribavirin

Recommended Monitoring

In addition to standard clinical and laboratory monitoring in a patient receiving Hepatitis C therapy, the following monitoring is recommended for telaprevir:

- **Hematologic adverse events (anemia):** Complete blood count with white blood cell differential counts should be obtained at baseline and at treatment weeks 4, 8, and 12, and at other time points, as clinically appropriate. Telaprevir treated patients experience an average hemoglobin decrease of approximately 3-4 g/dL (1 g/dL greater than seen with peginterferon and ribavirin alone). Initial management of anemia should consist of ribavirin dose reduction for hemoglobin <10g/dL or sooner if clinically indicated; for additional monitoring and management of Hepatitis C treatment-related anemia refer to the PBM CFU for Recombinant Erythropoietin.
- **Rash**:
    - Fatal and non-fatal serious skin reactions, including Stevens Johnson Syndrome (SJS), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), and Toxic Epidermal Necrolysis (TEN), have been reported in patients treated with INCIVEK combination treatment. Fatal cases have been reported in patients with progressive rash and systemic symptoms who continued to receive telaprevir combination treatment after a serious skin reaction was identified**. For serious skin reactions, including rash with systemic symptoms or a progressive severe rash, telaprevir, peginterferon alfa,**

and ribavirin must be discontinued immediately. Discontinuing other medications known to be associated with serious skin reactions should be considered. Patients should be promptly referred for urgent medical care.
    - Patients with mild to moderate rashes should be followed for progression of rash or development of systemic symptoms. If rash progresses and becomes severe (i.e. rash involving >50% of body surface area), telaprevir should be discontinued. Peginterferon alfa and ribavirin may be continued. If improvement is not observed within 7 days of telaprevir discontinuation, sequential or simultaneous interruption or discontinuation of ribavirin and/or peginterferon alfa should be considered. If medically indicated, earlier interruption or discontinuation of ribavirin and peginterferon alfa should be considered. Patients should be monitored until the rash has resolved. Telaprevir must not be reduced or restarted if discontinued due to rash. Treatment of rash with oral antihistamines and/or topical corticosteroids may provide symptomatic relief but effectiveness of these measures has not been established. **Treatment of rash with systemic corticosteroids is not recommended due to significant drug-interactions.**
- **Anorectal signs and symptoms:** The majority of these events (e.g., hemorrhoids, anorectal discomfort, anal pruritus, and rectal burning) were mild to moderate in severity. These symptoms resolved during or after completion of telaprevir.
- **Uric acid:** Elevated uric acid levels occurred more frequently in telaprevir-treated patients compared to treatment with peginterferon and ribavirin treatment alone (73% and 29%, respectively). Uric acid levels shifts of ≥12.1 mg/dL from baseline occurred in 7% of telaprevir-treated patients compared to 1% from control.The steepest increase in uric acid levels occurred during the first two weeks of treatment. In telaprevir-treated patients,<1% had clinical events of gout/gouty arthritis; none were serious or resulted in treatment discontinuation. Uric acid levels should be measured at baseline, weeks 2, 4, 8, 12 and as clinically indicated.
- **Bilirubin**: Elevated bilirubin levels occurred more frequently in telaprevir-treated patients compared to treatment with peginterferon and ribavirin alone (41% and 28%, respectively); 4% and 2% of patients, respectively, had ≥2.6 x ULN elevations. The steepest increase in bilirubin occurred during the first 1 to 2 weeks of telaprevir therapy. Bilirubin levels should be measured at baseline, weeks 2, 4, 8, 12 and as clinically indicated.
- **Response-guided therapy based upon HCV RNA levels:** HCV RNA levels should be measured at weeks 4, 12, and 24 of treatment or at other timepoints as clinically indicated.
- **Careful virologic monitoring** is required to assess when treatment is futile and should be halted to avoid the emergence of resistance. Prompt assessment of HCV RNA levels and treatment response is necessary to avoid resistance.
    - All treatment, including peginterferon and ribavirin, must be discontinued if any of the following occur:
        - HCV RNA is >1000 IU/mL at week 4 or 12
        - HCV RNA is detectable at week 24 or at any other timepoint thereafter
        - HCV RNA rebounds (≥1 $\log_{10}$ increase from the nadir HCV RNA) at any time while on treatment
- **Sustained Viral Response (SVR) or relapse** should be determined by measurement of HCV RNA at the end of therapy and 24 weeks thereafter.
- **Ongoing assessment of treatment adherence** including medical appointments, laboratory follow-up and medications should be performed.

Issues for Consideration

Treatment Considerations:

- For a more complete listing of pre-treatment considerations, refer to the VA HCRC and PHSHG HCV Treatment Recommendations.
- Chronic HCV-infected patients with minimal fibrosis (METAVIR stage 0, 1 based on an adequate liver biopsy specimen) are at lower risk for developing advanced liver disease in the short-term. After a thorough discussion of prognosis and treatment options, the provider and patient may agree to observation without treatment. Treatment should be reconsidered if liver disease progresses. Immediate HCV therapy should be considered in patients with acute HCV infection or extrahepatic manifestations of chronic HCV infection such as leukocytoclastic vasculitis, membranoproliferative glomerulonephritis, or symptomatic cryoglobulinemia despite mild liver disease. Minimal fibrosis cannot be assumed in the absence of a liver biopsy or an inadequate biopsy specimen.
- Providers may decide to treat genotype 1 patients with only peginterferon and ribavirin depending on individual patient characteristics. Refer to Monograph for clinical data on IL-28B status as a pre-treatment consideration.
- Telaprevir should not be dose-reduced. If telaprevir is discontinued, it should not be restarted.
- **If ribavirin is discontinued secondary to adverse event(s), then telaprevir should also be discontinued to avoid development of resistance.**

Use in Specific Populations (refer to Prescribing Information for comprehensive list of use in specific populations):

- Substance or Alcohol Use: Patients with a history of substance or alcohol use who are abstinent should be considered for treatment. There are no published data supporting a minimum length of abstinence as an inclusion criterion for HCV anti-viral treatment. Patients with active substance or alcohol use disorder who are willing to participate in a substance use program should be considered for therapy on a case-by- case basis.
- Hepatitis B: No safety and efficacy data are available in this population; pharmacokinetic studies demonstrate concomitant administration of tenofovir and telaprevir resulted in similar telaprevir exposure but higher tenofovir exposure. Prescribing information recommends that increased clinical and laboratory monitoring are warranted and tenofovir should be discontinued in patients who develop tenofovir-associated toxicities.
- HIV: There are limited safety or efficacy data available in this population and there are significant drug-drug interactions with certain antiretroviral agents.
- Solid Organ transplant: No efficacy and safety data available in this population and there are significant drug-drug interactions with certain immunosuppressants.
- Renal Impairment: No dosage adjustment is necessary for patients with mild, moderate or severe renal impairment; telaprevir was not studied in patients with end-stage renal disease or on hemodialysis.
- Hepatic Impairment: Telaprevir exposure is reduced by 53% in patients with Child-Pugh B hepatic impairment; telaprevir should not be administered to patients with moderate to severe hepatic impairment (Child-Pugh Class B or C, score ≥7)

Drug-interactions:

- Telaprevir is a strong inhibitor of CYP3A4 and substrate of P-glycoprotein. Drugs metabolized primarily by CYP3A4 may have increased exposure when administered with telaprevir, which could increase or prolong their therapeutic and adverse effects. Coadministration of telaprevir with drugs that induce or inhibit CYP3A4/5 could decrease or increase exposure to telaprevir.
- Pharmacokinetic studies of concomitant administration of telaprevir and oral contraceptive therapy have shown decreased levels of oral contraceptives. Therefore, oral contraceptives may be ineffective with concomitant administration of telaprevir.

Hepatitis C Education and Screening:

- Counsel patient on general liver health, especially abstaining from alcohol use.
- Assess if patient previously screened and/or vaccinated for Hepatitis A and Hepatitis B vaccines; consideration vaccination if appropriate.
- Assess if patient previously screened for HIV; if not, consider testing for HIV.

Additional Resources:

- Refer to VA Office of Public Health Intranet Site http://vaww.hepatitis.va.gov for additional resources
- Refer to the VA HCRC and PHSHG HCV Treatment Recommendations, "Management and Treatment of Hepatitis C Viral Infection: Recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office" for additional information (PDF available at http://vaww.hepatitis.va.gov).

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